



FIGHTING
INFECTIOUS
DISEASES
FOR
SEVEN
DECADES

THE PUBLIC HEALTH RESEARCH INSTITUTE
at the International Center of Public Health

RUTGERS
New Jersey Medical School

Pharmacokinetics in Pulmonary Lesions/MALDI-MS Imaging Studies of Drug Distributions

Brendan Prideaux
PHRI, Newark, NJ

9th National Conference on Laboratory Aspects
of Tuberculosis
June 9th



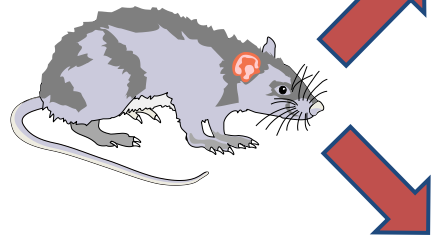
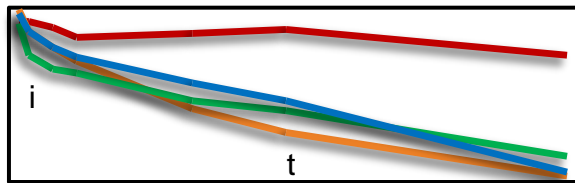
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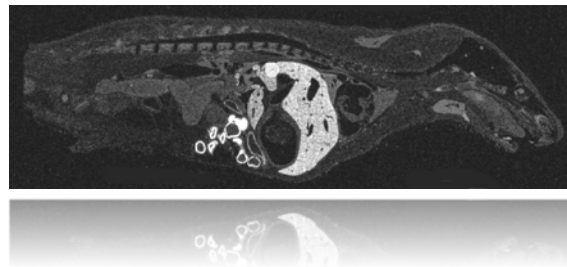
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Analytical methods for drug distribution

PK/Metabolism

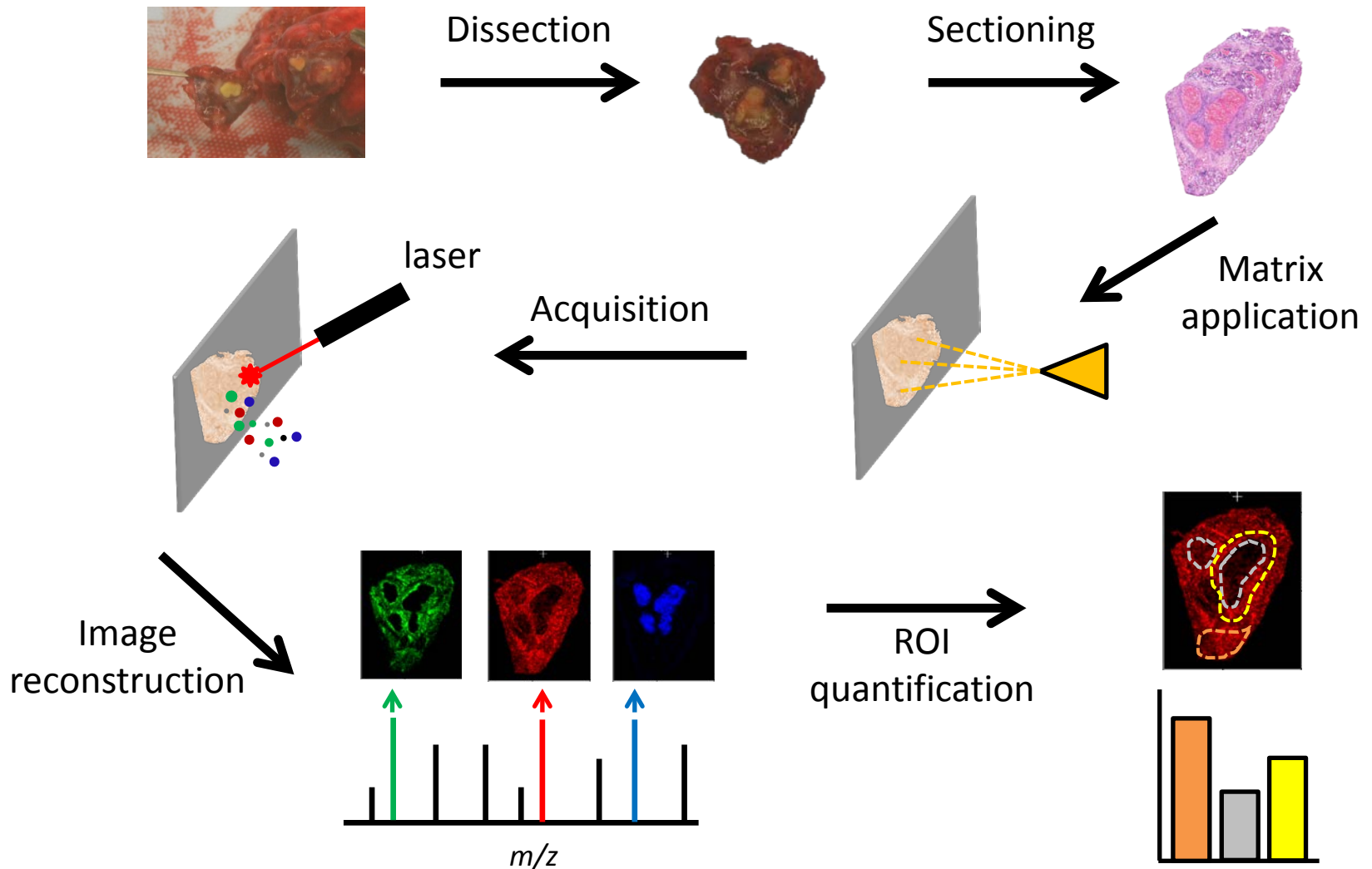


Distribution



- dissection of animal
- limited spatial resolution
- only parts of animal
- label required
- total radioactivity
- not specific

MALDI-MSI



Semi-Quantitation

Co-crystallization of
matrix/analyte/internal
standard?

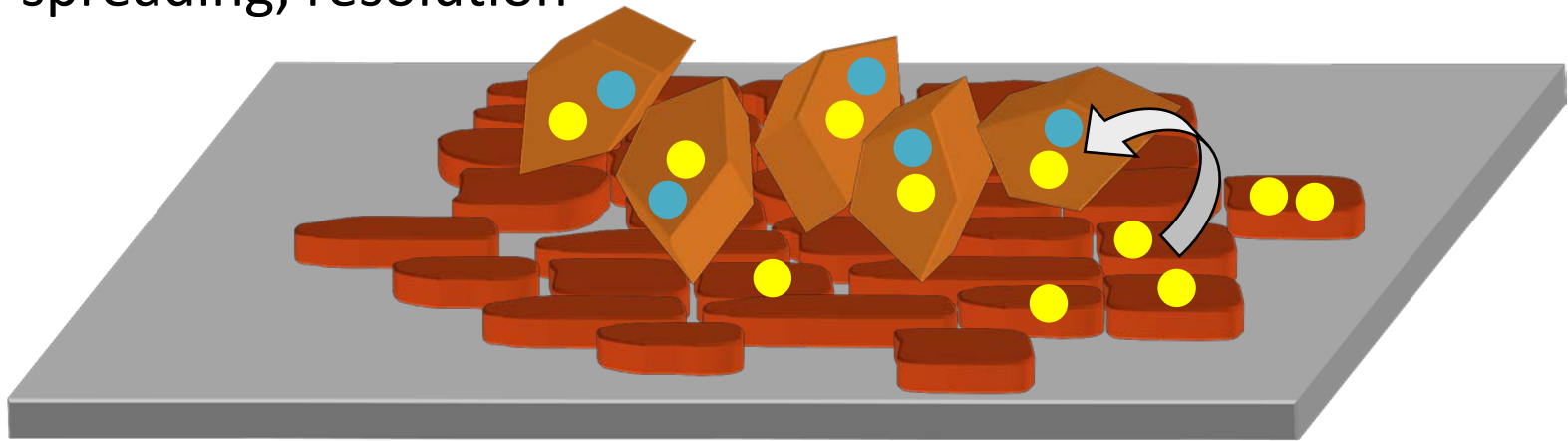
⇒ solvation of analyte

⇒ spreading, resolution

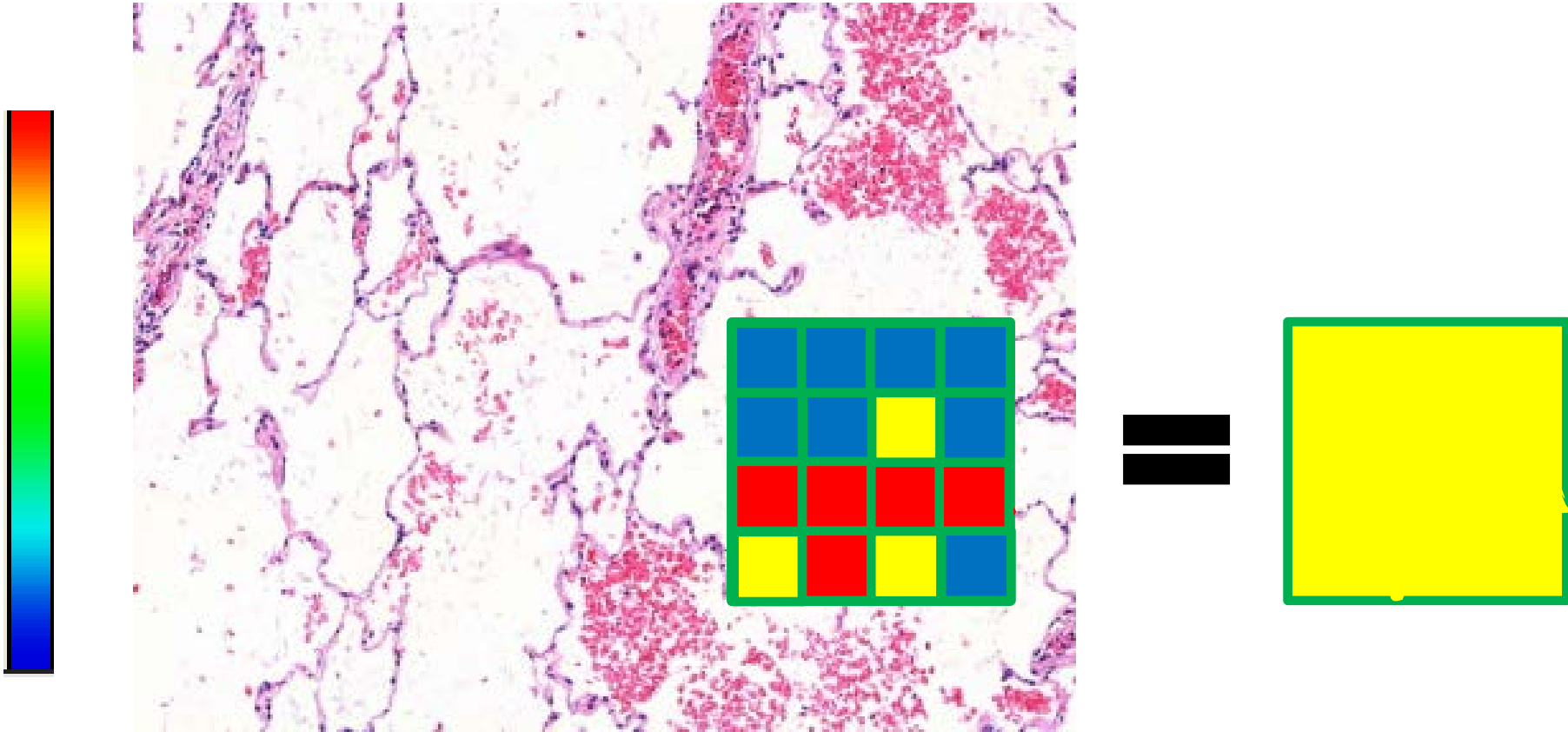
Crystal size

⇒ sensitivity

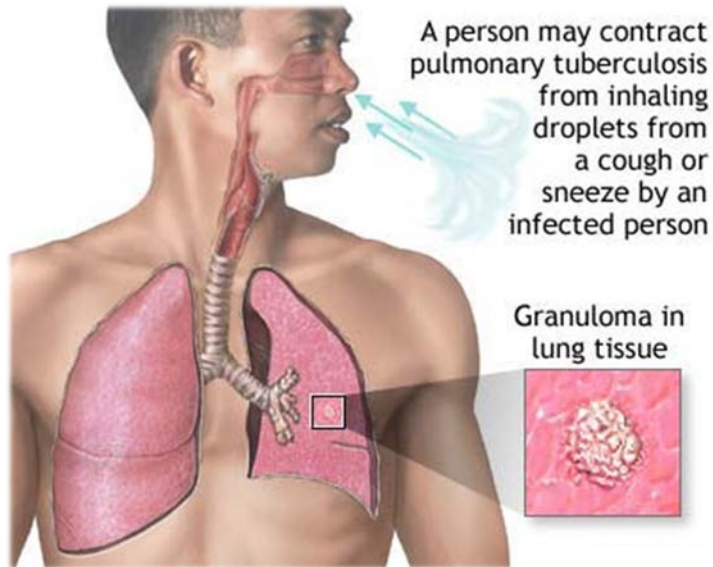
⇒ image resolution



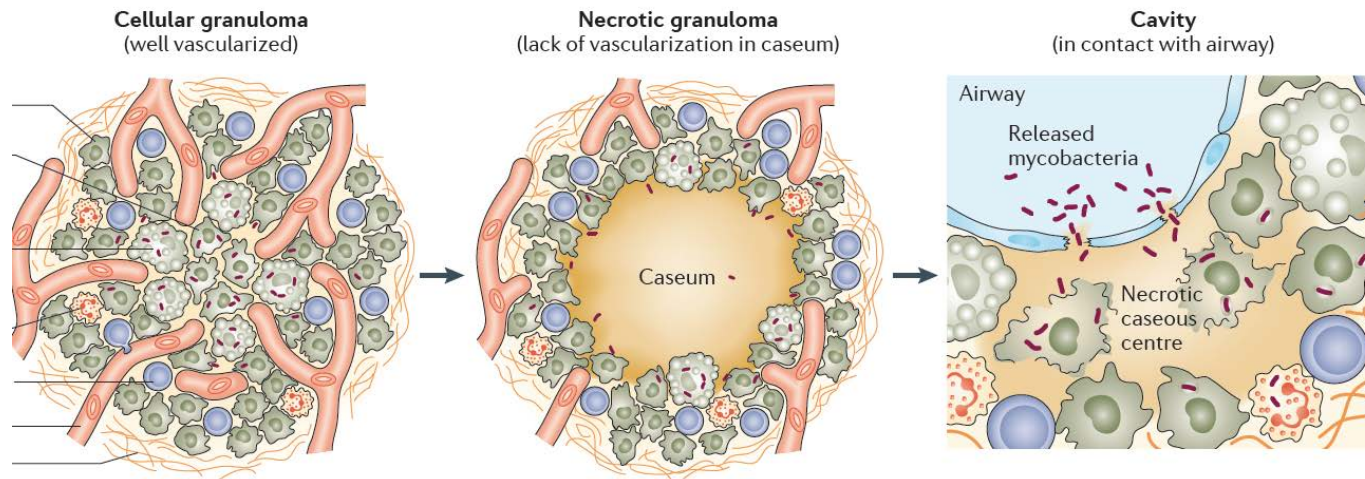
Importance of spatial resolution – laser averaging



The need to assess lesion drug penetration



- Existing drug regimens were developed before standard PK measurements existed
- Need to optimize dosing regimens of existing TB drugs (concentrations and combinations)
- Use detailed lesion penetration information for developing novel anti-TB compounds

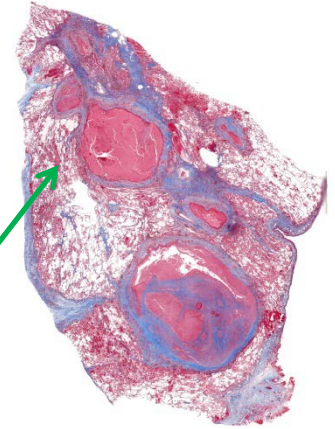


Clinical pathology

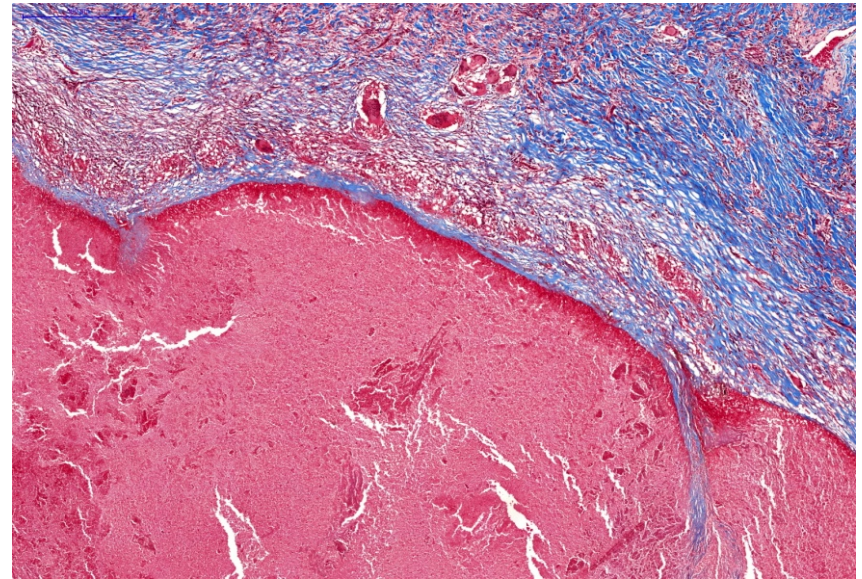
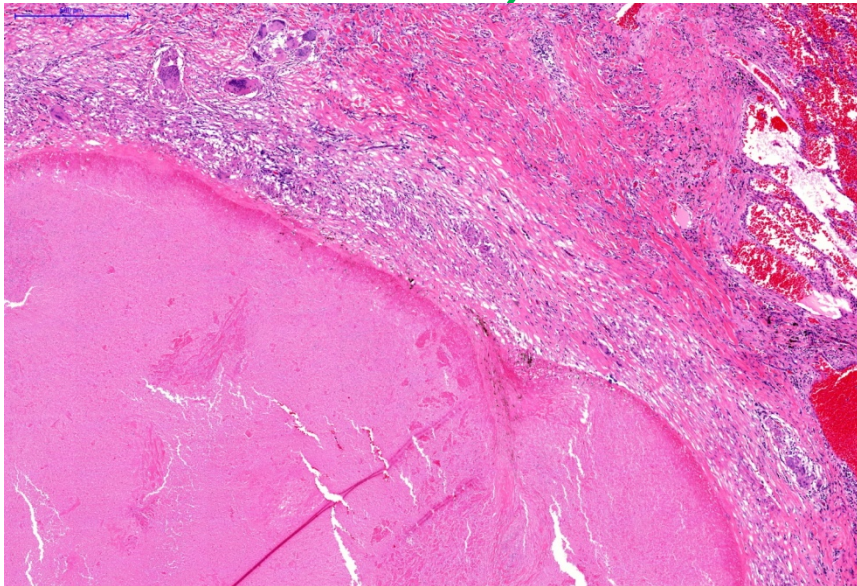
1000 µm



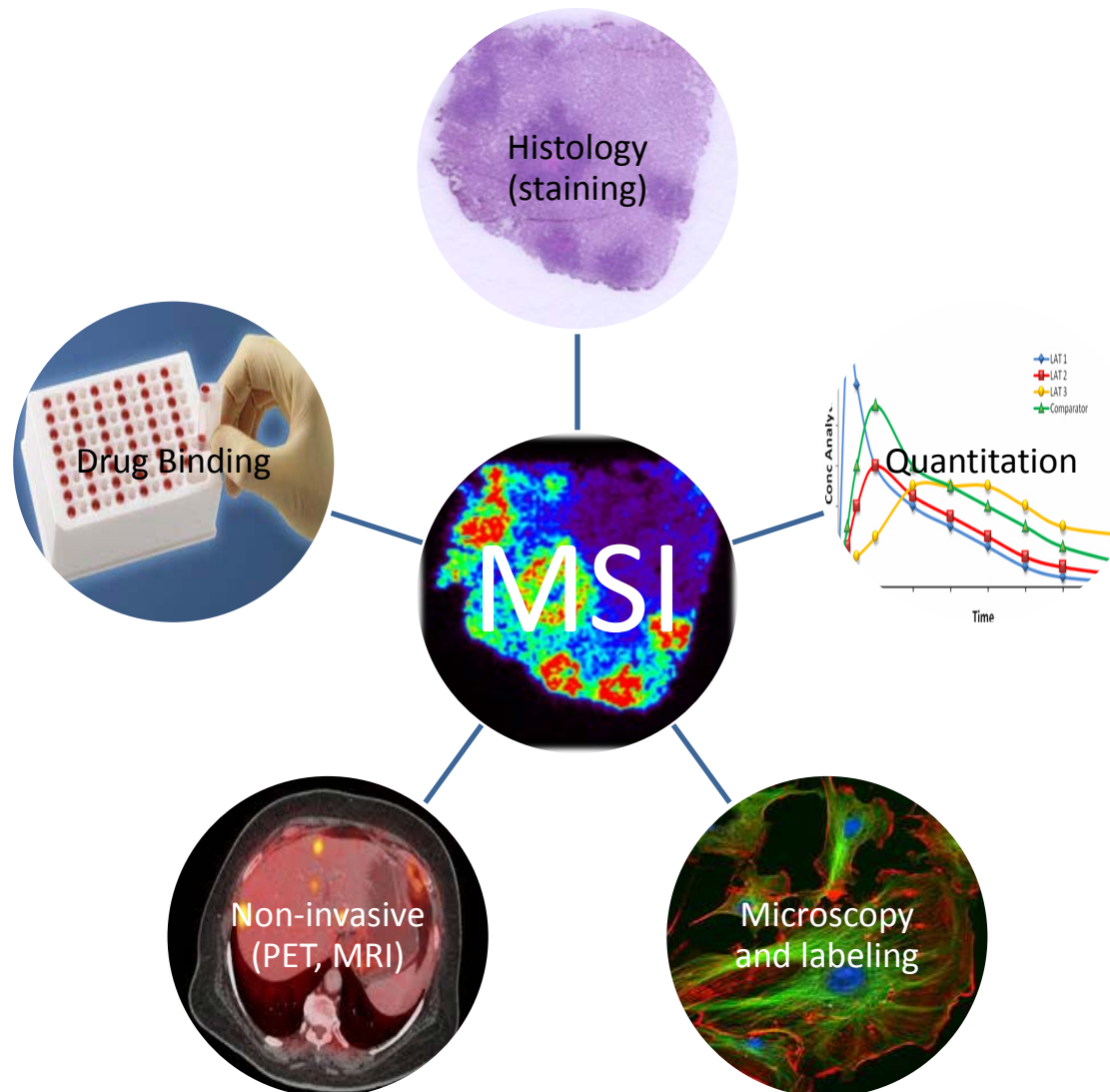
H&E



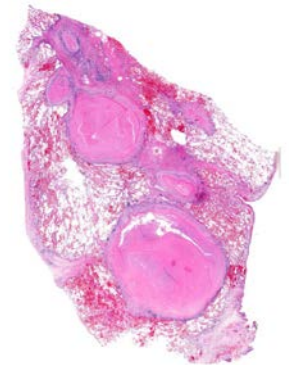
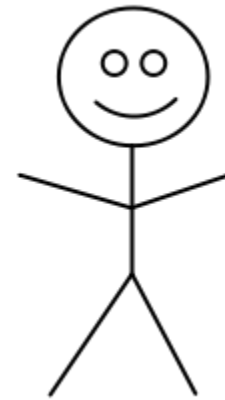
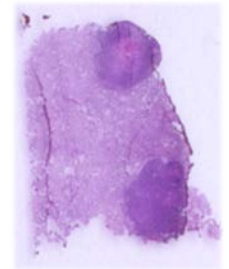
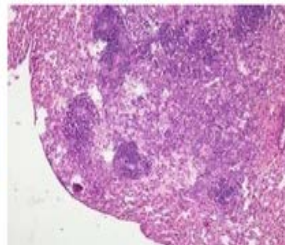
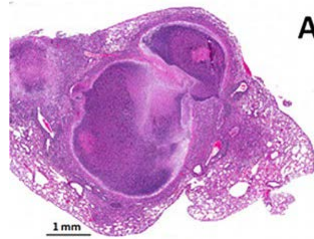
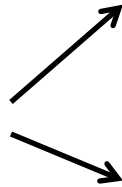
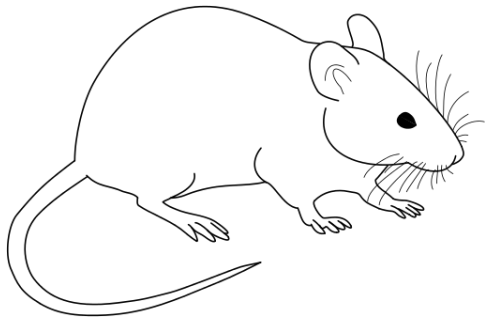
Massan Trichrome



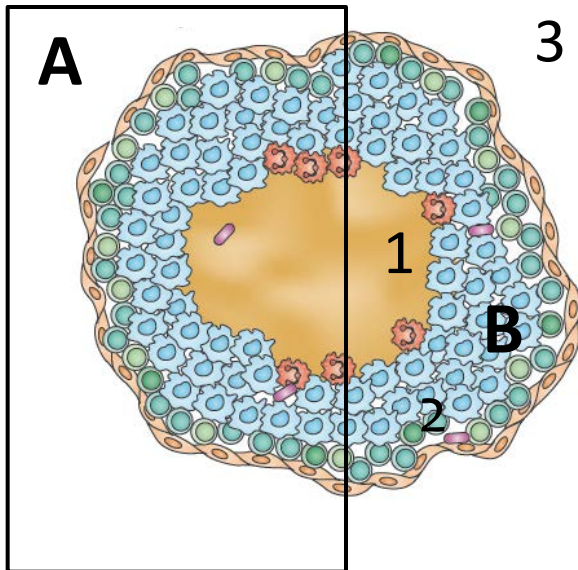
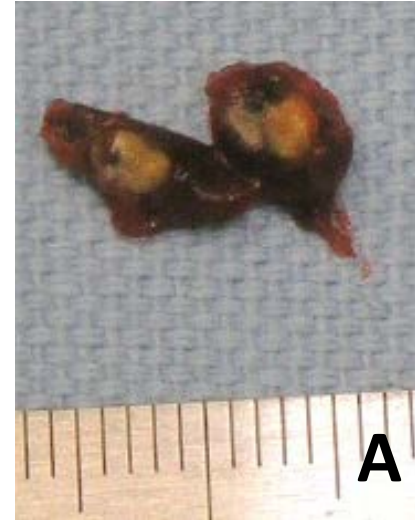
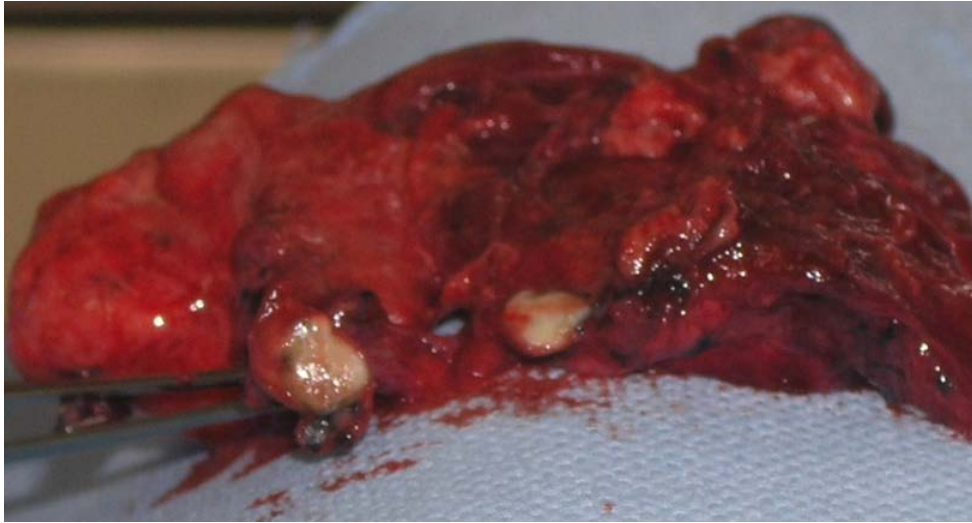
Multi-modal lesion studies



Animal Models



Lesion processing



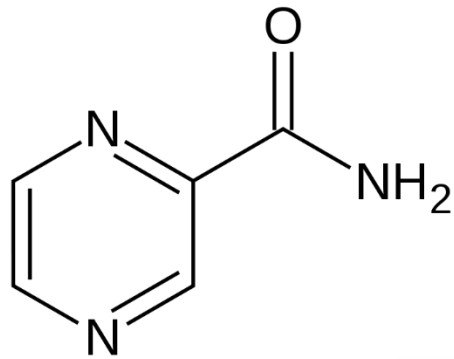
A. Sample for Imaging MS

Snap-frozen with surrounding tissue
-> 2D map of drugs by MALDI-TOF

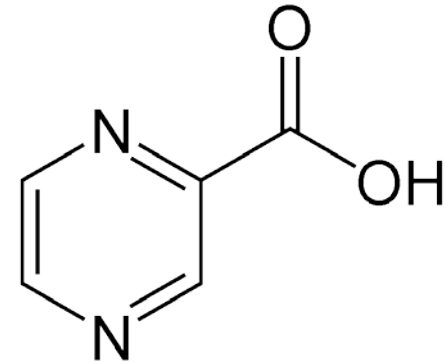
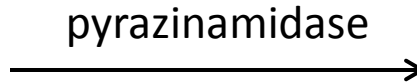
B. Sample for Drug Quantitation by MS

Dissected out (if cavity, caseum and wall processed separately)
Weighed and frozen

Pyrazinamide



MW 123.113



MW 124.10



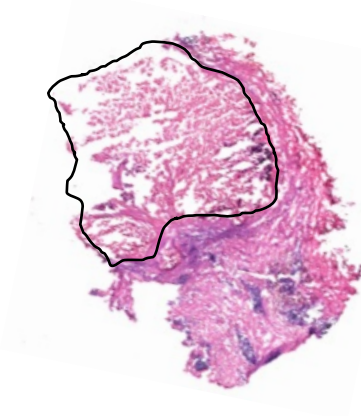
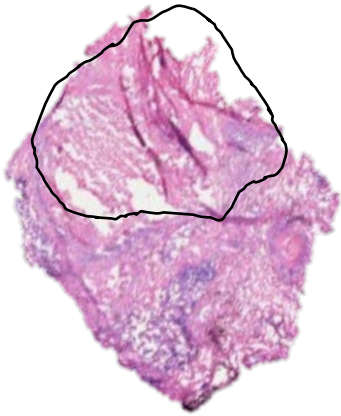
Clinical (1500mg)

3.3h

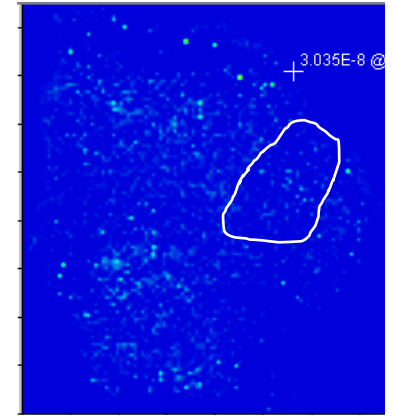
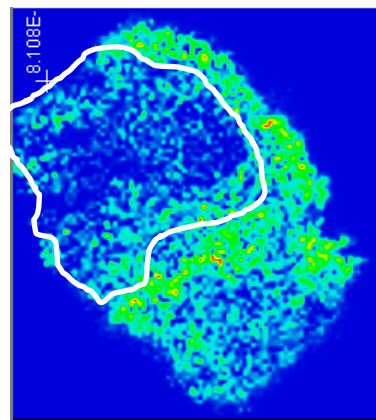
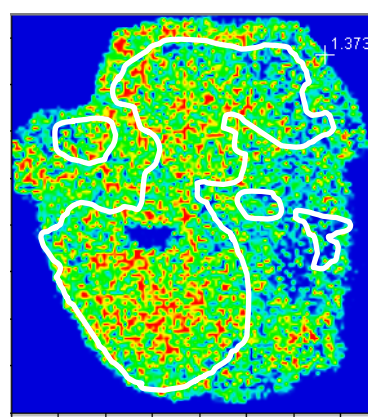
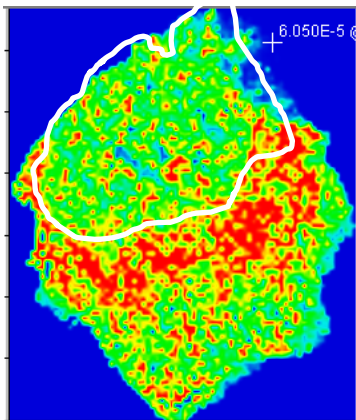
5h

11h

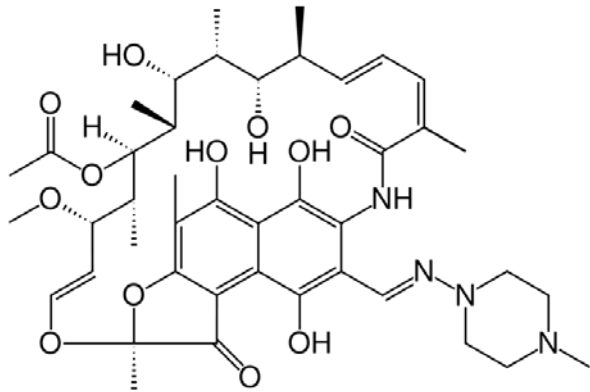
24h



PZA



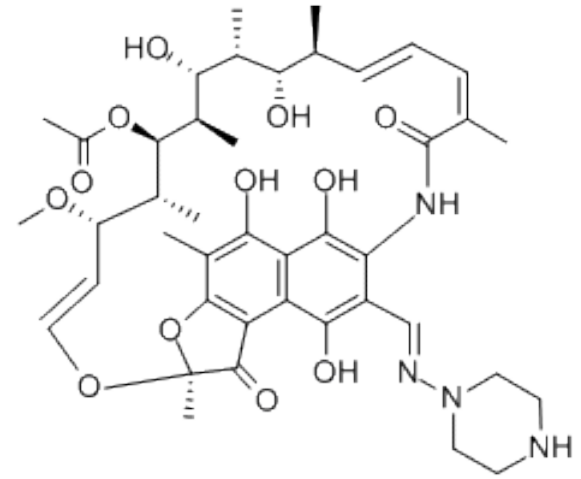
Rifampicin



MW 822.94



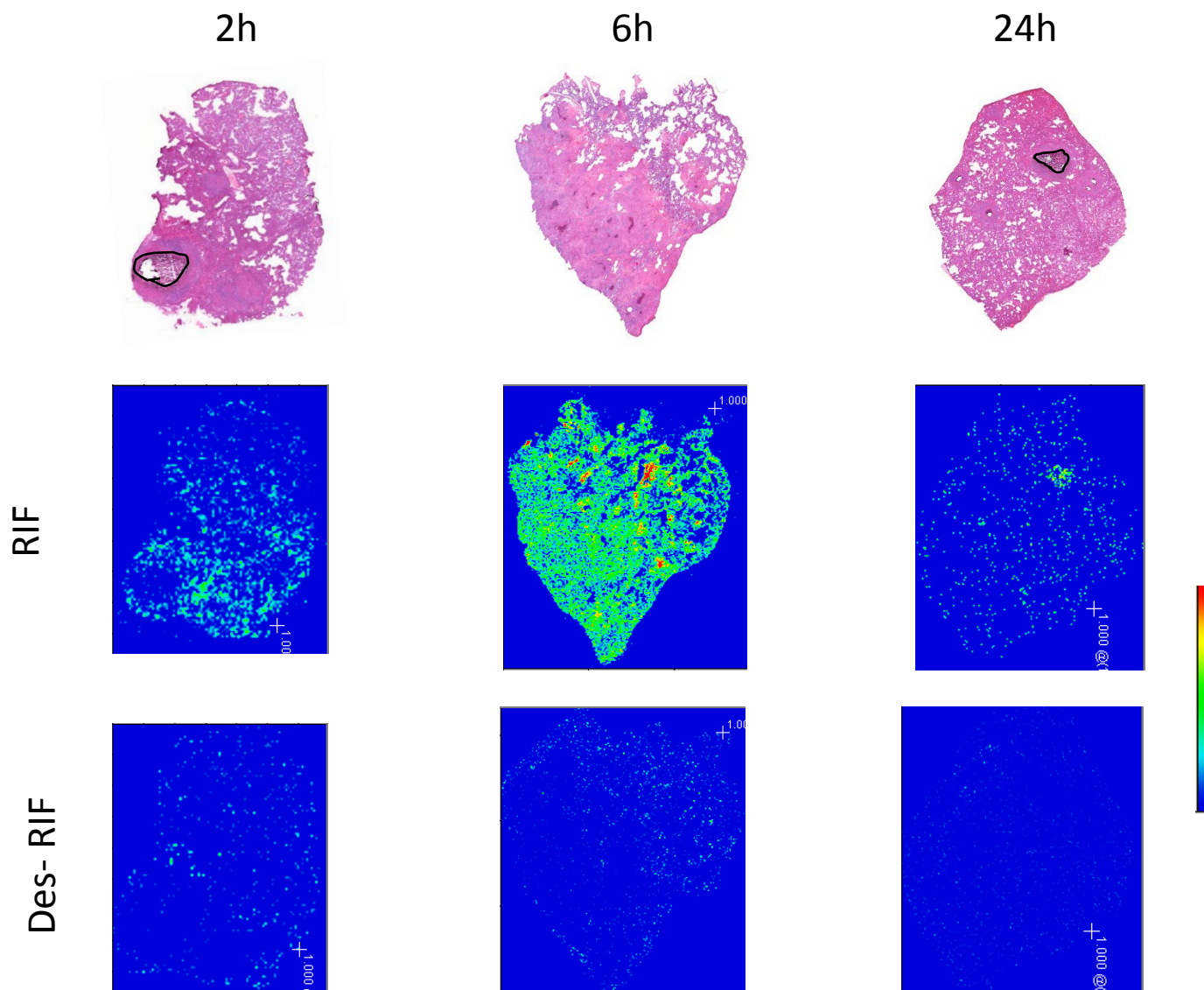
Des acetyl
rifampicin



MW 780.90



Rabbit (30mg/kg)



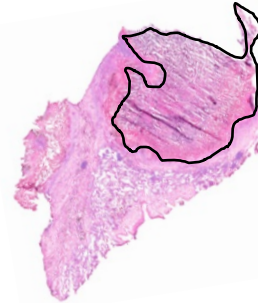
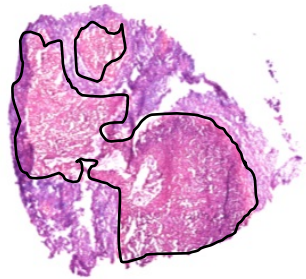
Clinical (600mg)

2h

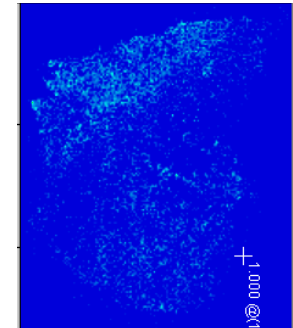
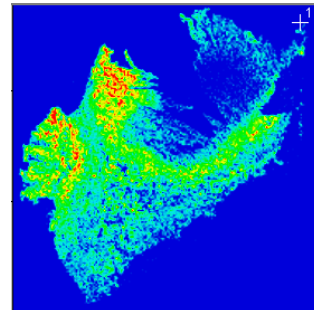
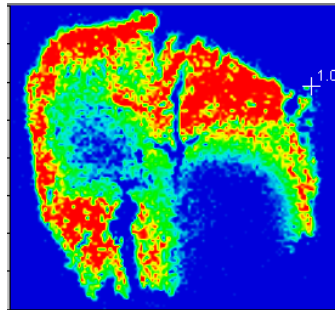
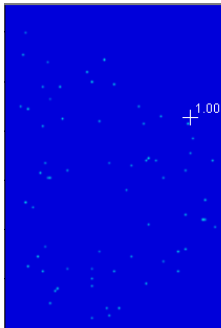
5h

11h

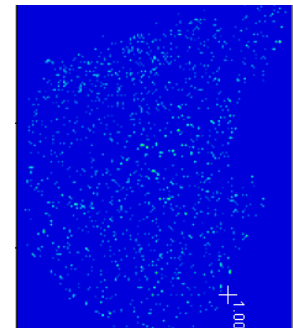
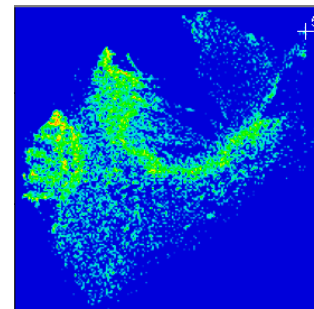
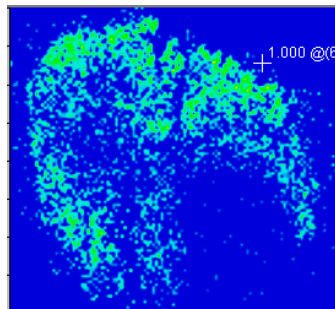
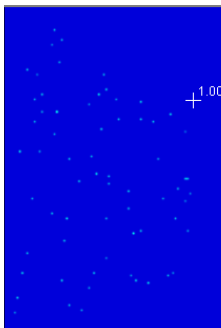
22h



RIF

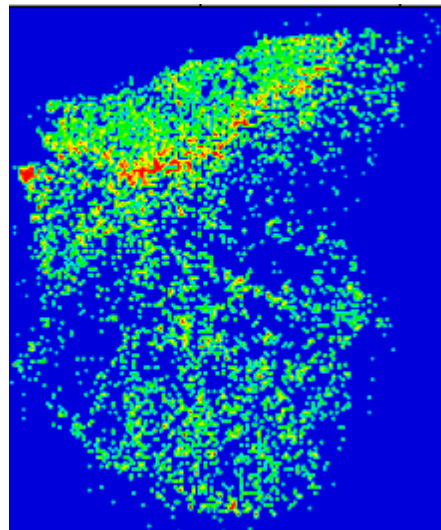
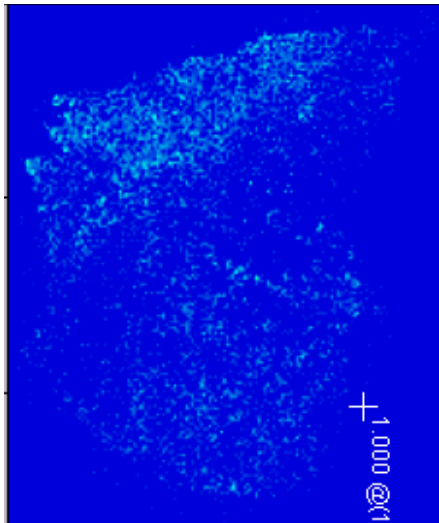


Des-RIF

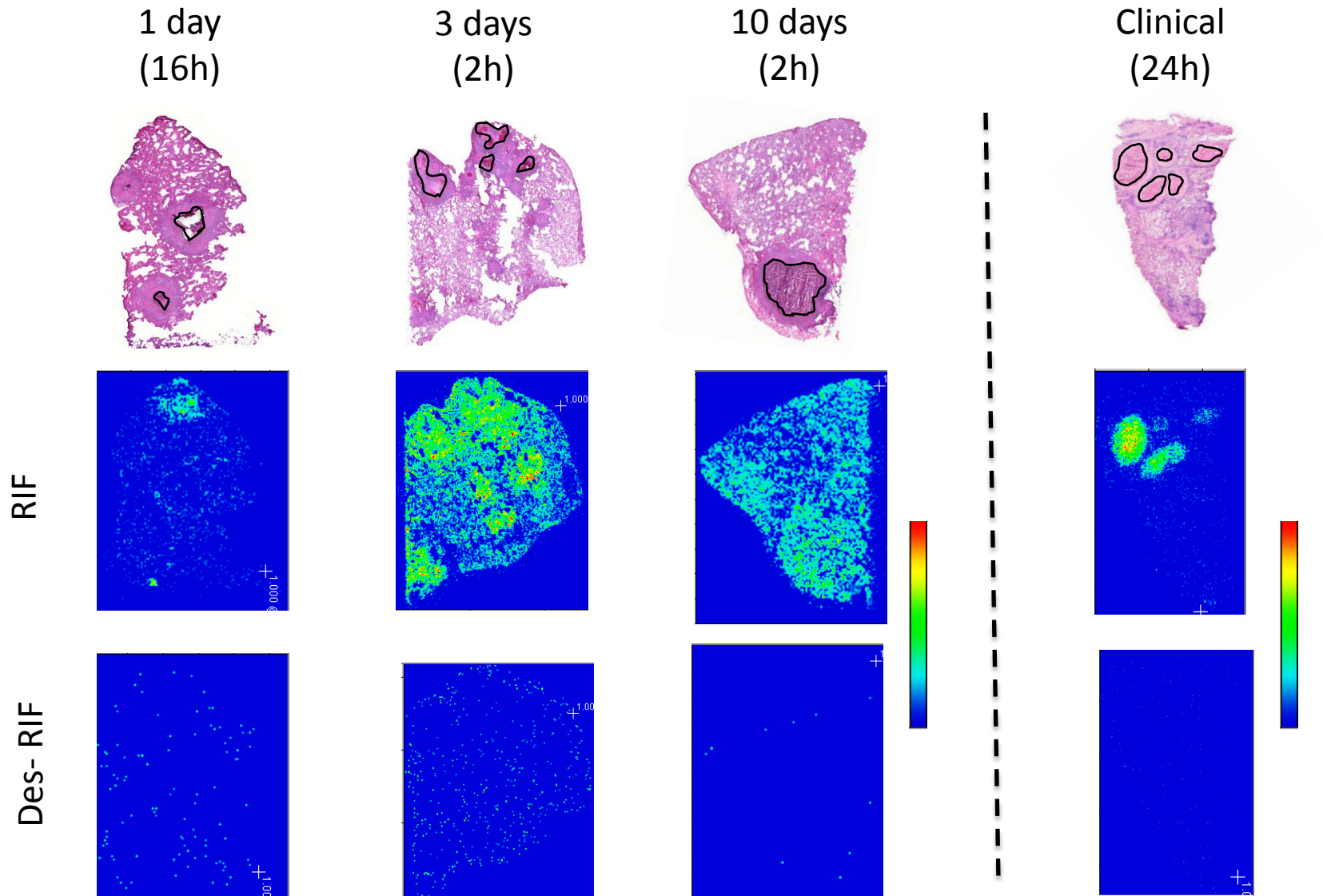


Penetration of RIF into caseum at late timepoints

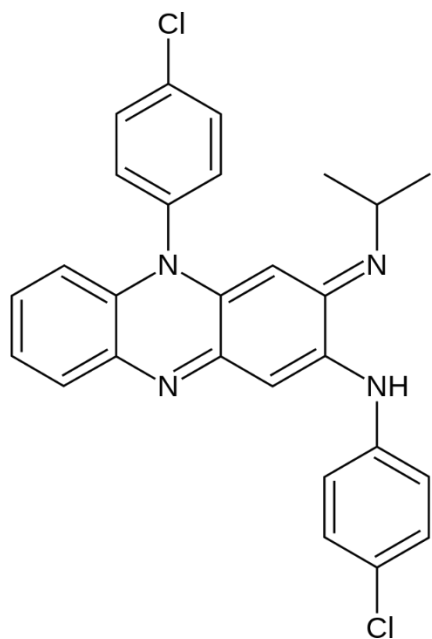
22h



Steady-state dosing



Clofazimine

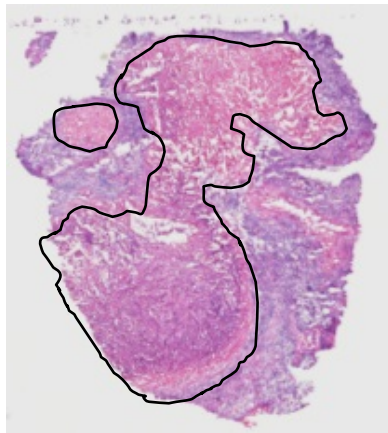


MW 473.396

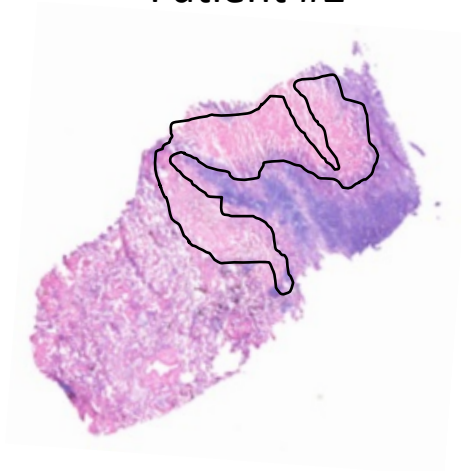


Clinical (steady-state)

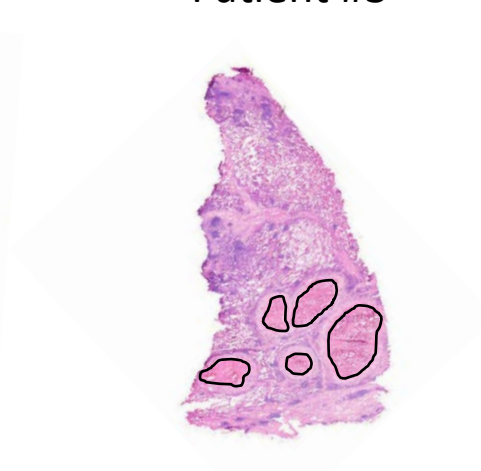
Steady-state
Patient #1



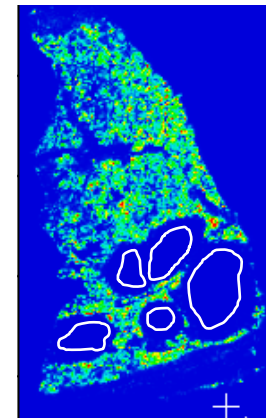
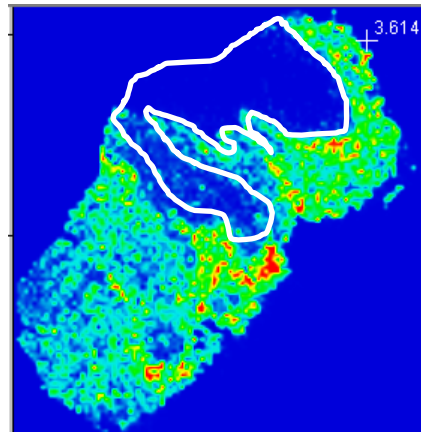
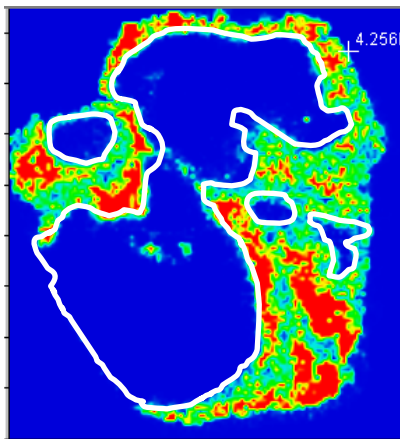
Steady-state
Patient #2



Steady-state
Patient #3



CFZ

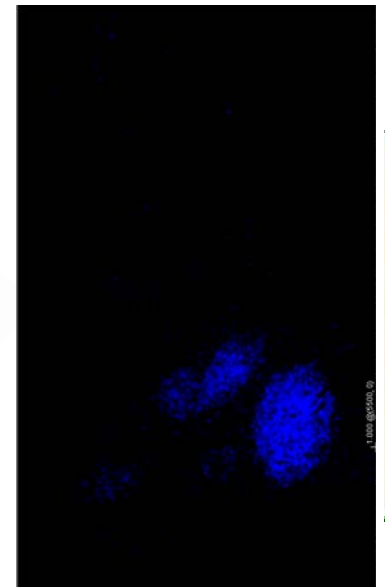
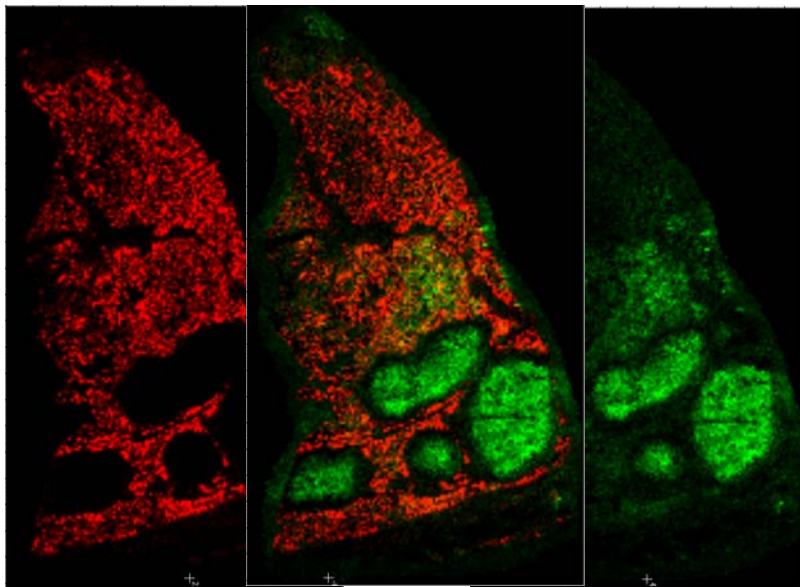


Clofazimine v RIF distribution

Clofazimine

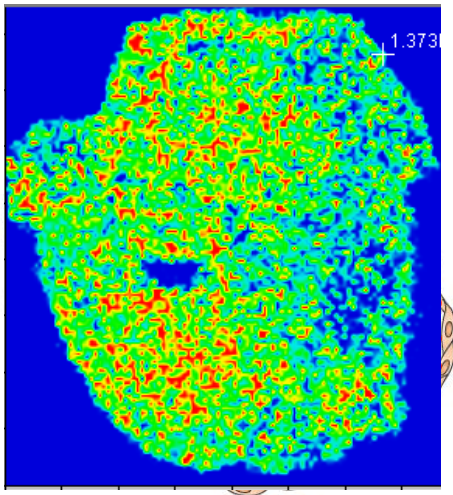
Cholesterol

Rifampicin



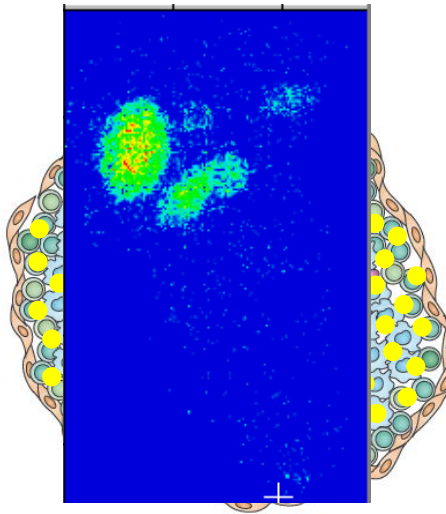
Summary

Rapid diffusion
into caseum, rapid
elimination



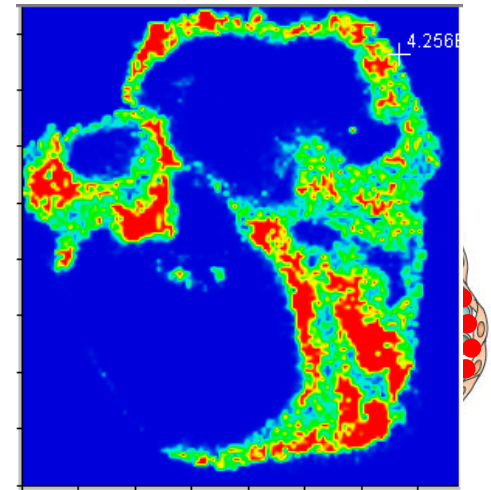
PYRAZINAMIDE

Slow caseum
penetration and
accumulation



RIFAMPICIN

Poor to no
caseum
penetration



CLOFAZIMINE

Lesion distribution information is important for optimizing existing therapies and developing novel drugs!!!



- Veronique Dartois
- Pei-Yu Chen
- Matt Zimmerman
- Jansy Sarathy
- Hsin-Pin Ho
- Paul O'Brien
- Firat Kaya
- Isabella Freedman



- Anne Lenaerts
- Scott Irwin
- Mike Lyons



- Cliff Barry
- Laura Via
- Danielle Weiner